Challenges in the hemodynamic management of acute nontraumatic neurological injuries

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Purpose of review
To appraise the evidence from the literature and suggest an integrated hemodynamic approach of early and delayed phases of acute ischemic stroke (AIS), subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH).

Recent findings
In AIS, the research aims to evaluate the optimal pressure control before, during and after the revascularization, to optimize the perfusion in the ischemic areas, minimizing the risk of hemorrhage or secondary damage to already infarcted areas. In the early phase of SAH, systemic pressure should be controlled to balance the risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressure. The late phase aims to minimize the risk of cerebral vasospasm by adapting systemic pressure and volemia to cerebral and systemic physiological hemodynamic targets. In the mild-to-moderate ICH, achieving SAP of less than 140 mmHg and greater than 110 mmHg may be considered as a beneficial target. Caution should be considered in lowering intensively SAP in severe ICH.

Summary
In nontraumatic brain injuries, the hemodynamic management is strictly related to fluctuating physiology of these diseases, needing a strict control of pressure and flow variable to ensure both cerebral and systemic homeostasis.

Keywords
fluid therapy, hemodynamic monitoring, ischemic stroke, subarachnoid hemorrhage

INTRODUCTION

Fluid management and hemodynamic optimization in patients with acute brain injury (ABI) is challenging because of several physiological peculiarities compared with nonbrain-injured ICU patients. In general ICU patients, clinical strategies and pathways to optimize hemodynamics by means of clinical examination and more advanced hemodynamic monitoring are quite established [1]. Moreover, recent findings support to avoid fluid overload or promote fluid 'restriction' in general ICU patients, especially those admitted for sepsis/septic shock [2]. Interestingly and very recently, a large prospective, multicenter, comparative effectiveness study on 2125 patients enrolled in two observational cohorts of traumatic brain-injured patients (CENTER-TBI in Europe and OzENTER-TBI in Australia), showed that also in these patients a mean positive daily fluid balance was associated with higher ICU mortality and worse functional outcome per 0.1 l increase [3].

On the contrary, clinical strategies of hemodynamic management of nontraumatic ABI are still based on moderate/low-quality evidence retrieved from relatively small studies, as reported in the most updated consensus/recommendations on these topics [4–7]. Both the hemodynamic monitoring/targets and fluid management/balance should consider the physiological peculiarities of ABI patients, in particular those affected by an acute cardiac dysfunction associated with sympathetic stimulation and catecholamine release [7].

The purpose of this review is to appraise existing guidelines and contemporary literature on hemodynamic management of acute ischemic stroke (AIS),

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KEY POINTS

- In the AIS, the pressure targets suggested by the guidelines may be adapted to the degree of reperfusion achieved after clot removal.
- During endovascular treatment of AIS, MAP thresholds of less than 70 mmHg for more than 10 min or greater than 90 mmHg for more than 45 min are associated to poor functional outcomes.
- In the early phase of SAH, a SAP pressure threshold less than 160 mmHg is reasonable.
- The evidence regarding the hemodynamic management of the late phase of SAH is still conflicting; however, some indicators (such as the global end-diastolic volume index) may be useful in optimizing systemic volemia.
- In the mild-to-moderate ICH, achieving SAP of less than 140 mmHg and greater than 110 mmHg may be considered as a beneficial target. Caution should be considered in lowering intensively SAP in severe ICH.

subarachnoid hemorrhage (SAH), spontaneous intracerebral hemorrhage (AIH) and intracerebral hemorrhage (ICH), including both pressure/flow management and fluid homeostasis (amounts and types of fluids and volume and circulatory status monitoring).

ACUTE ISCHEMIC STROKE

AIS is one of the most impacting disease globally, having a significant effect on long-term morbidity, and in turn, on health and financial systems worldwide [8]. In the last decades, new therapies have been introduced to improve outcomes, primarily aiming for the early recognition and revascularization of the occluded vessel [9].

It is possible to split the pathophysiology and the treatment of AIS (including hemodynamic management) between the phase characterized by the sudden loss of blood flow to a specific area of the brain with the resulting loss of neurologic function (related to thrombosis or embolism occluding a cerebral vessel), and the phase following the reperfusion of ischemic tissue with intravenous thrombolysis or intravascular clot removal.

As a consequence, blood pressure management is challenging as the initial need of improving tissue perfusion in the ischemic areas should be balanced against the increased risk of hemorrhage or secondary damage to already infarcted areas of the brain because of elevated pressure.

The correct blood pressure management during the early phase of the AIS or once reperfusion is achieved is still debated. The recent 2019 American Stroke Association/American Heart Association (ASA/AHA) acute stroke guidelines recommend:

(1) In patients with blood pressure less than 220/120 mmHg who did not receive intravenous thrombolysis or endovascular treatment and had no comorbid conditions requiring acute antihypertensive therapy, the benefit of initiating or reinitiating treatment of hypertension within the first 48–72 h is uncertain. It might be reasonable to lower blood pressure by 15% during the early phase [10▪▪] (Table 1).
(2) Blood pressure less than 185/110 mmHg in patients who are candidates for either intravenous thrombolysis or endovascular treatment [10▪▪] (Table 1 and Fig. 1).

However, in 2015, a metanalysis of 13 randomized controlled trials showed that blood pressure lowering in early AIS did not affect the risk of disability or death, all-cause mortality, recurrent stroke, and serious adverse events or dependency at 3 months [11].

In 2019, a large prospective, multicenter cohort study on 485 patients identified a systolic arterial pressure (SAP) peak after the endovascular treatment of 158 mmHg as the best discriminating good from bad AIS functional outcome (i.e. patients with a peak higher than this threshold had an increased likelihood of having a bad outcome in unadjusted, but not in adjusted analysis) [12].

In the same year, a multicentric trial randomly assigned 2196 patients within 6 h of stroke onset to receive intensive (target SBP 130–140 mmHg within 1 h, or guideline (SAP < 180 mmHg) blood pressure-lowering treatment over 72 h. Fewer hemorrhages occurred in the intensive therapy group but the authors found no difference in long-term clinical outcomes [13].

Another critical issue is the SAP target considering the degree of reperfusion achieved after the endovascular treatment. Once a successful recanalization is obtained, the optimal postoperative SAP threshold may be lower than that stated by the guidelines to minimize the risk of reperfusion injury. In a multicentric study, Anadani *et al.* [14] enrolled 1245 patients from 10 stroke centers and found that those with higher SAP after successful reperfusion had lower odds of achieving good results and higher odds of symptomatic intracerebral hemorrhage, mortality, and need for hemicraniectomy than patients in the reference group (121–140 mmHg).

Finally, intraprocedural endovascular blood pressure management seems to be an essential and modifiable therapeutic target to prevent or minimize the risk of poor functional outcomes. In

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Table 1. Acute ischemic stroke and subarachnoid hemorrhage hemodynamic management in early and late phases

	Initial assessment	Intraprocedural	Late phase management
AIS			
Pressure	BP may be permitted up to 220/120 mmHg in patients who are not candidates for either IV t-PA or IAT and do not have another contraindication to an elevated BP [10▪▪]. BP <185/110 mmHg in patients who are candidates for either IV t-PA infusion or IAT [10▪▪].	Avoid MAP less than 70 mmHg for more than 10 min [15▪]. Avoid MAP less than 40% of baseline values [18]. Avoid MAP greater than than 90 mmHg for more than 45 min [15▪]. SAP between 140 and 180 mmHg [19].	For patients who received IV t-PA therapy, it is recommended that the BP be maintained below 180/105 mmHg for the following 24 h [10▪▪]. Consider maintaining high BP in patients with incomplete reperfusion (TICI 0–2a) [20]. SAP less than 140/160 mmHg in patients with complete reperfusion (TICI 2b–3) [21].
Flow	No specific recommendations available	No specific recommendations available	No specific recommendations available
Concerns	Despite the lack of a lower limit of BP in the guidelines, hypotension is associated with worse outcome	Monitor neurological fluctuations to target high/low BP values	Monitor neurological fluctuations to target high/low BP values
SAH			
Pressure	Between the time of SAH symptom onset and aneurysm obliteration, SAP should be controlled [4]. For unsecure aneurysm SAP less than 160 mmHg or MAP less than 110 mmHg are reasonable targets [4,5]	No specific indications. SAH treatment includes surgical/nonsurgical approaches for different phenotypes of source of bleeding	Pharmacological strategies to prevent DCI therapy are commonly associated to hypotension, requiring the use of vasopressors to maintain a sufficient MAP, especially in case of continuous IV infusion
Flow	No specific indications	No specific indications	Preload functional index (i.e. GEDI) may be useful to optimize volemia. Hypovolemia should be avoided.
Concerns	A decline in the neurological function may be related also to cardiopulmonary cause (i.e. neurogenic pulmonary edema, catecholamine cardiomyopathy manifesting with hypoxia and/or hypotension). Echocardiography may be useful to rule out cardiomyopathy in the acute phase	Clinical changes associated MAP fluctuations may be related to exceeding the lower limit of autoregulation or unbalanced ICP increase	The evidence still provides conflicting results regarding specific hemodynamic strategies aimed at preventing CV
ICH			
Pressure	SAP less than 140 mmHg and greater than 110 mmHg in patients with mild-to-moderate ICH	In ICH patients requiring neurosurgical treatment, intraoperative hypotension (<100 mmHg) has to be avoided	Target SAP 130–140 mmHg for at least 7 days
Flow	No specific indications	No specific indications	No specific indications
Concerns	Caution should be considered in lowering intensively SAP in severe ICH	No specific indications	No specific indications

AIS, acute ischemic stroke; BP, blood pressure; CV, cerebral vasospasm; DCI, delayed cerebral ischemia; GEDI, global end-diastolic volume; IAT, intra-arterial thrombectomy; ICH, intracranial hemorrhage; ICP, intracranial pressure; MAP, mean arterial pressure; SAH, subarachnoid hemorrhage; SAP, systolic arterial pressure; TICI, The Thrombolysis in Cerebral Infarction score; t-PA, type plasminogen activator.

a very recent study enrolling 365 patients, Rasmussen *et al.* [15▪] found that poor functional outcomes were associated with a mean arterial blood pressure (MAP) thresholds of less than 70 mmHg for more than 10 min or greater than 90 mmHg for more than 45 min. This study raises two crucial clinical issues: it suggests that MAP is more sensitive than SAP in the assessment of clinically relevant changes in brain perfusion, and secondarily, encourages the use of reliable and continuous monitoring (maybe invasive) to detect and correct potentially harmful MAP fluctuations (Table 1).

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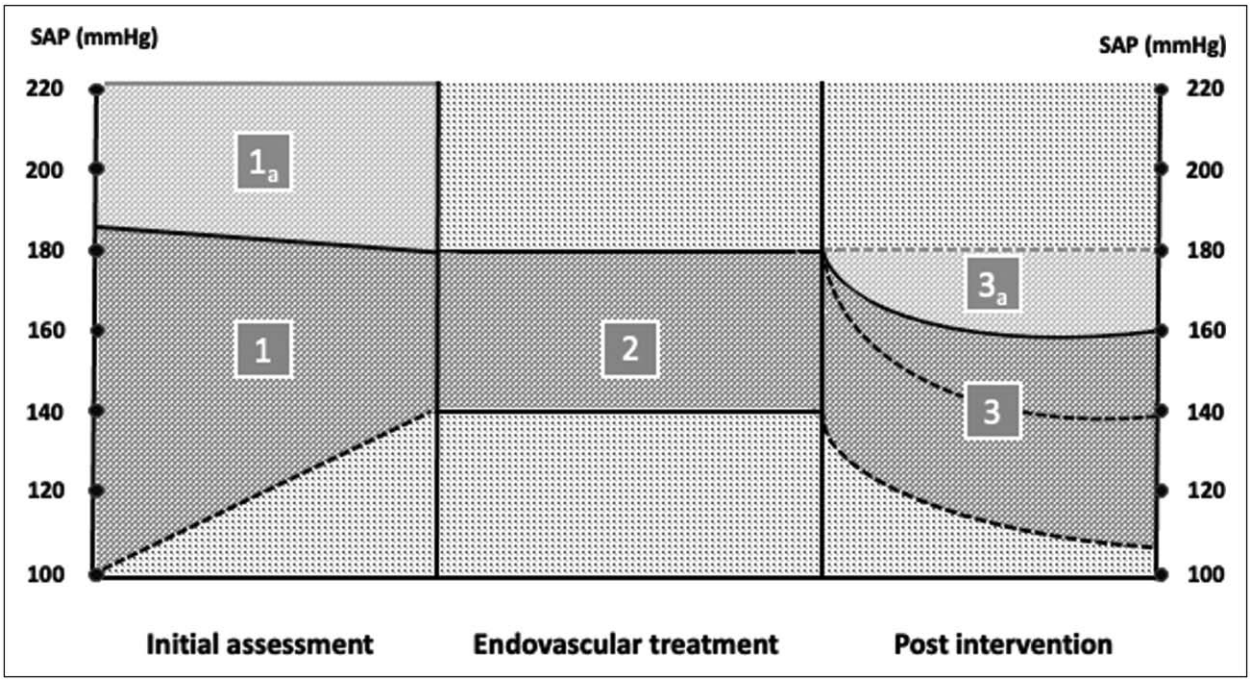

FIGURE 1. Schematic systolic arterial pressure management during in-hospital phases of AIS, according to the most updated evidence of the literature (see references provided in Table 1). Phase 1 – initial assessment: SAP targets BP less than 185/110 mmHg in patients who are candidates for either intravenous type plasminogen activator infusion or intra-arterial thrombectomy (phase 1_a – SAP targets up to 220/120 mmHg in patients who are not candidates for active therapies and have no contraindications to elevated SAP). At this step, hypotension is associated with worse outcomes and should be avoided. Phase 2 – revascularization: SAP between 140 and 180 mmHg. Phase 3 – postintervention: SAP 140/160 mmHg in patients with complete reperfusion (phase 3_a – SAP maintained below 180/105 in patients with incomplete reperfusion. At this step, relative hypotension after successful reperfusion may reduce the risk of secondary injury. SAP management should consider neurological fluctuations and systemic signs of organs' hypoperfusion.

SUBARACHNOID HEMORRHAGE

Hemodynamic management early phase

Quite intuitively, uncontrolled hypertension is risk factor of bleeding exacerbation and rebleeding of an unsecured intracranial aneurysm. The risk of this complication, which is associated with increased mortality and a worsened functional recovery prognosis, is maximal in the first 2–12 h after the first event, and the rate of occurrence ranges between 4 and 14% within the first 24 h [4,16]. A retrospective review of 273 SAH patients by Ohkuma *et al.* [17] showed the risk of rebleeding for those with an SAP greater than 160 mmHg was significantly higher (odds ratio 3.1, 95% confidence interval 1.5–6.8).

There is general agreement that acute hypertension should be controlled after SAH and until the aneurysm is secured; however, thresholds for blood pressure control are still undefined. The most recent guidelines for the management of aneurysmal subarachnoid hemorrhage from the AHA/ASA recommend the following targets [4]:

(1) Between the time of SAH symptom onset and aneurysm obliteration, blood pressure should be controlled with a titratable agent to balance the risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressure (Class I, Level B) [4].
(2) The magnitude of blood pressure control to reduce the risk of rebleeding has not been established but a decrease in SAP pressure to less than 160 mmHg is reasonable (Class IIa, Level C) [4] (Table 1).

The Neurocritical Care Society stated that modest elevations in blood pressure with a MAP less than 110 mmHg does not require therapy [5] (Table 1).

Several different mechanisms should be considered in the hemodynamic management of the early phase of SAH. First, the ICP may be raised because of the presence of mechanical factors (such as hydrocephalus and the volume of intracranial bleeding itself) or altered cerebral autoregulation leading to global cerebral hypoperfusion [22]. Moreover, an acute cardiac systolic or diastolic dysfunction has

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been described in 2–15 and 46–89% of SAH patients, respectively [7].

Hemodynamic management of delayed phase

Cerebral vasospasm refers to transient, self-limited constriction of the intracranial arteries, typically occurring between days 4 and 14 after an aneurysmal subarachnoid hemorrhage (SAH). Cerebral vasospasm may be detected by either neuroradiologic findings of arterial narrowing or by specific patterns seen by the intracranial Doppler [23].

Cerebral vasospasm is associated with clinical deterioration caused by delayed cerebral ischemia (DCI) and can affect up to 30– 40% of patients, leading to DCI in 20–30% of cases [24]. Angiographic cerebral vasospasms have been considered the leading cause of DCI; however, more recently, some other mechanisms (i.e. microvascular spasm, microthrombosis, cortical spreading depolarization, and failure of cerebral autoregulation) have been implicated as being involved [25].

Historically, the management of the cerebral vasospasm is mainly based on both the hemodynamic optimization of the systemic MAP as part of the 'triple H' approach (hypertension, hypervolemia, and hemodilution) [26] to ensure cerebral perfusion despite the constriction of the intracranial arteries and on pharmacological interventions to minimize the pathological vascular response.

This concept has been challenged in the last 15 years. In fact, in a pivotal experimental study, Muench *et al.* investigated the effect of the three components of triple-H therapy under physiologic conditions, showing that vasopressor-induced elevation of MAP caused a significant increase in regional cerebral blood flow and brain tissue oxygenation. In contrast, volume expansion slightly affected regional cerebral blood flow only but reversed the effect on brain tissue oxygenation [27].

To date, there is no specific medical strategy to prevent the occurrence of DCI. However, nimodipine (a dihydropyridine L-type calcium channel blocker) reduces the risk of poor neurological outcomes, oral administration is recommended for all SAH patients [28]. This therapy is commonly associated with hypotension as a hemodynamic side effect, requiring the use of vasopressors to maintain a sufficient MAP, especially in the case of continuous intravenous infusion [29].

Significantly few randomized trials investigated the clinical effect of different hemodynamic strategies to reduce cerebral vasospasm incidence employing fluid administration or vasoactive agents. Optimal hemodynamic strategy after SAH can be challenging, and evidence is still lacking. Almost 10 years ago, Rondeau *et al.* randomized 35 patients of single center to norepinephrine-induced hypertension vs. dobutamine-induced elevated cardiac index as a preventive strategy, showing no difference in the incidence of radiographic vasospasm [30]. Interestingly, 12 (70%) patients in the dobutamine group also received norepinephrine to ensure a CPP greater than 60 mmHg because of blood pressure lowering [30].

Regarding the fluid management after SAH, a post hoc analysis of the CONSCIOUS-1 trial [31] showed that the use of colloids for volume expansion was borderline associated with worse neurological performance status [National Institutes of Health Stroke Scale (NIHSS) scale >10 (dichotomization threshold chosen roughly as a moderate disability for each scale); $P = 0.042$] [32]. Interestingly, multivariate analysis including only patients with severe angiographic vasospasm showed a borderline significant interaction between vasospasm severity and fluid balance ($P = 0.048$). In fact, a negative fluid balance was found to be associated with greater incidence of delayed infarcts (OR 0.13, 95% CI 0.02–0.57; $P = 0.013$) [32].

On the contrary, the results of a recent small randomized-pilot trial (20 patients) and a previous review suggest that hypervolemia may be associated to adverse events [33,34].

Therefore, targeting euvolemia is challenging in SAH patients, especially as the balance between pressure and flow targets should consider both the effects inside and outside the brain. For these reasons, feasible and reliable hemodynamic parameters may be useful at the bedside to track the effects of different strategies. In 2013, a multicenter prospective cohort study explored the hemodynamic variables of 204 SAH patients (including 138 with poor grade SAH and 52 who developed DCI) and monitored by using a transpulmonary thermodilution system (PiCCOplus) [35]. In patients with DCI, the global end-diastolic volume index (GEDI), was significantly lower than in those without DCI on days 3–5 ($P = 0.0053$; $P = 0.048$ and $P = 0.048$), respectively and was associated to onset of DCI [35].

In another multicentric prospective study, a GEDI threshold value of 822 ml/m^2, slightly above the reference range, was not only shown to be protective against DCI development but also associated with the occurrence of pulmonary oedema (hazard ratio, 1.31; 95% CI 1.02–1.71; $P = 0.03$) [36].

Overall, these results emphasize the challenging balance of increasing circulating volume to improve brain perfusion, combined with the occurrence of systemic side hemodynamic effects in SAH patients

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with a well recognized risk of developing myocardial injuries [37].

However, in high-risk SAH patients, it is still suggested a background fluid infusion of 1500–4000 ml/day [7,38] to maintain a cardiac output greater than 3 l/min (by also using albumin or dobutamine infusion in case of decline) and a GEDI greater than 680 ml/m^2, as main hemodynamic targets [7].

Regarding the type of fluids, there is a general agreement in avoiding hypotonic fluids (Class III, evidence level B – AHA/ASA SAH guidelines (2012) [4]) and isotonic crystalloid should be considered the preferred agent for volume replacement (moderate quality evidence; weak recommendation – Neurocritical Care Society recommendations on critical care management in SAH (2011) [5]).

INTRACRANIAL HEMORRHAGE

ICH refers to nontraumatic bleeding in the brain parenchyma. This condition is associated to poor acute (1-month case-fatality rate of ~40% with limited improvement in this outcome in the last few decades) and long-term neurological outcome, with most survivors having residual severe disability.

The hemodynamic management of ICH is primarily focused on blood pressure control as uncontrolled high SAP is associated with hematoma expansion and worse clinical outcome [39]. Despite previous concerns related to the risk of lowering blood pressure after ICH, because of the need of ensuring adequate cerebral perfusion, more recent data showed that an intensive early blood pressure reduction (SAP target 110–139 vs. 140–179 mmHg) was well tolerated but without functional or mortality benefit [40]. However, a more recent preplanned pooled meta-analysis analysis of individual participant (3829 patients) of the two large trials showed that achieving early and stable SAP of 120–130 mmHg results in improvements in functional recovery in mild-to-moderate ICH [41▪▪]. Accordingly, the European Stroke organization has recommended lowering SAP less than 140 mmHg and greater than 110 mmHg in patients with ICH [42].

These hemodynamic targets, however, should be considered with caution in patients with large and severe ICH. In fact, a recent post hoc analysis of the Antihypertensive Treatment of Acute Cerebral Hemorrhage-II trial was performed on 999 patients who underwent randomization and had an initial SAP value. Among 228 participants with initial SBPs of 220 mmHg or more, those randomized to intensive (vs. standard) SAP treatment had a higher rate of neurological deterioration within 24 h [15.5 vs. 6.8%; relative risk, 2.28 (95% CI, 1.03–5.07); $P = 0.04$] despite having no benefits in reducing death or 90 days severe disability [43▪].

CONCLUSION

Hemodynamic management of the AIS focuses on choosing the optimal MAP/SAP pressure before, during, and after the revascularization. The early phase of SAH requires active and prompt SAP control to reduce the risk of rebleeding. In contrast, the late-stage aims to minimize the risk of cerebral vasospasm by adapting systemic pressure and volemia to cerebral and systemic physiological hemodynamic targets. In the mild-to-moderate ICH, achieving SAP of less than 140 mmHg and greater than 110 mmHg may be considered as a beneficial target. Caution should be considered in lowering intensively SAP in severe ICH.

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